Cytokines And Left Ventricular Remodeling In Patients With Chronic Coronary Artery Disease

A.L.Alyavi, Z.T.Sabirjanova, D.K.Tulyaganova, J.K.Uzokov, D.I.Radjabova, S.K.Nuritdinova, T.Khan, L.Yunusova

Cardiology Department, Republican Specialized Scientific-Practical Medical Center for Therapy and Medical Rehabilitation, Tashkent, Uzbekistan

Abstract— **The study was carried out to establish the prognostic value of post-infarction (PI) cardiac remodeling and cytokine imbalance for the development of chronic heart failure (CHF) in patients with coronary artery disease (CAD) with the enrolling 55 patients with the history of Q wave myocardial infarction (MI). For of development of CHF in patients with PI myocardial remodeling the clinical picture, cardio hemodynamic indicators and laboratory markers will allow to identify the maladjusted LV model in the early stages of the disease and to develop new pathogenically based treatment methods for this pathology.**

Keywords— left ventricular remodeling; post myocardial infarction; cytokine; coronary artery disease.

I. Introduction

Coronary heart disease (CHD) is one of the main causes of heart failure, which is accompanied by remodeling of the left ventricular (LV) myocardium [1]. Myocardial remodeling with the loss of cardiomyocytes, the development of interstitial fibrosis, accompanying myocardial hypertrophy and ischemic heart disease, ultimately leads to systolic and diastolic dysfunction of the left ventricular myocardium [21]. However, studies have shown that, despite the improvement in the clinical status of patients and the decrease in cardiovascular risk with the use of blockers of these systems, ischemic heart disease continues to progress [1,4,6,16]. It is not clear that there is a possibility of a cardiovascular risk of coronary artery disease [18]. According to the progresses and progresses of the synthesis of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and others, which, in turn, determine myocardium remodeling [10,11,12,15,19].

Pro-inflammatory cytokines play an important role in the progression of the disease [9], mainly influencing LV dysfunction, the intensity of myocardial and vascular remodeling processes by controlling the level of cardiomyocyte apoptosis, which in turn is considered as a fundamental mechanism determining the development of contractile and possibly diastolic myocardial dysfunction [1,2,5,7,8].

The modern concept of the pathogenesis of coronary artery disease accumulates in itself all the above theories based on their complementarity, since one cannot rely on the fact that with one seemingly quite logical concept of pathogenesis one can explain all disorders in a patient with heart failure and moreover solve all problems of therapy, affecting the only mechanism for the development and progression of circulatory failure [3,4,13,14,16,20].

In connection with the above, it seems relevant to study the relationship of cytokine imbalance with the pathogenetic mechanisms of post infarction myocardial remodeling and the determination of their prognostic value during post infarction heart failure in patients with IHD.

Aim: To establish the prognostic value of post-infarction cardiac remodeling and cytokine imbalance in the clinical course of chronic heart failure in patients with coronary artery disease.

Materials and methods: 55 patients were examined, the average age was 54.1 ± 9.8 years. Among them, 37 men and 18 women. All patients in the history suffered myocardial infarction with Q of the left ventricle of various localization, from two to seven years. All patients had signs of circulatory insufficiency II-III FC by NYHA. II FC by NYHA - 35 patients, III FC - 20 patients. The control group was included 25 IHD and CHF. All patients, taking into account the functional class, comorbidity, age, received standard therapy for CHF: ACE inhibitors, β-blockers, angiotensin receptor antagonists, diuretics, antiplatelet agents. All patients underwent general clinical and biochemical blood tests, standard ECG and special studies.

The processes of cardiac remodeling, ischemic dysfunction of the LV myocardium with the identification of local abnormalities of the contractile function were determined using the EchoCG method on a Samsung medison ultrasound device Accuvix.V20 (Korea) using a sector sensor with a color mode and a pulse-wave, continuous-wave mode with a frequency of 2 -4 MHz in standard echocardiographic positions. A set of echocardiographic parameters was determined for each patient: calculation of LV remodeling indices, indicators characterizing its systolic function, and values estimating LV preload.

The study of the content of cytokines, endothelin-1 and vascular endothelial growth factor was carried out by the enzyme immunoassay using the apparatus Humareader Single (Germany).

The quality of life of all patients was assessed using the University of Minnesota questionnaire,

designed specifically for patients with CHF T. Rector, J. Cohn (MLHFQ). The result was evaluated by the sum of points: the best quality of life corresponds to 0, and the worst - 105 points.

Statistical processing. The results were processed using the statistical data analysis package of the STATISTICA 6.0 program and the Biostat software package.

Results: Features of cardiohemodynamics and clinical course of chronic heart failure II and III FC by NYHA in various options for post-infarction remodeling.

In the study were included 55 patients who had Q myocardial infarction with CHF II and III FC by NYHA. Men prevailed in this group of patients (67.2% of men and 32.7% of women).

Using the criteria Gottdiener J.S. et al. (1994), the following types of LV remodeling were identified: normal geometry, eccentric hypertrophy with LV dilatation, eccentric hypertrophy without LV dilatation, concentric LV hypertrophy (table 1).

Table 1

Types of left ventricular remodeling in the examined patients

Indicators	Normal geometry (n-11)	Eccentric hypertrophy with dilation (n-14)	Eccentric hypertrophy without dilation (n-13)	LV concentric hypertrophy (n-12)
LVMM	<200 gr. – m < 150 gr. – f	>200 gr. – m > 150 gr. – f	>200 gr. – m > 150 gr. – f	>200 gr. –m > 150 gr. – f
LVMMI, g/m2	< 102 gr. – m < 88 gr. – f	> 102 gr. – m > 88 gr. – f	> 102 gr. – m > 88 gr. – f	> 102 gr. – m > 88 gr. – f
RVTI LV	< 0,45	< 0,45	< 0,45	≥ 0,45
ISs	0,4 - 0,45	0,4 - 0,45	> 0,45	0,4 - 0,45
ISd	0,55 - 0,65	0,55 - 0,65	> 0,65	0,55 - 0,65
EDVI, ml/m2	< 97	< 97 ml/m2	> 97 ml/m2	< 97ml/m2
ESVI, ml/m2	< 49	< 49 ml/m2	> 49 ml/m2	< 49 ml/m2
EDSI, см/m2	< 3,1 cm/m2	≤ 3,1	> 3,1 cm/m2	≤ 3,1 cm/m2

When analyzing morphometric parameters (LV myocardium mass (LV MM), LV myocardium mass index (LVMMI), sphericity index in systole (ISs), sphericity index in diastole (ISd), relative wall thickness index LV (RVTI), end - diastolic volume (EDVI), end-systolic volume index (ESVI), end-diastolic size index (EDSI)) noted that among patients of FC III, individuals with LV remodeling of eccentric hypertrophy with and

without dilatation of its cavity predominate. In this group of patients, the end - diastolic volume is 105 ± 17 ml. In all groups of patients with CHF III FC in comparison with similar indicators of patients with CHF II FC there was a decrease in RVTI (p <0.01).

Thus, it was established that the result of this structural adjustment is the formation of special LV models - like eccentric hypertrophy with dilatation and without LV dilatation, which is accompanied by a worsening clinical features of CHF.

Analysis of central hemodynamic parameters in patients with various types of myocardial remodeling showed that in all studied groups there was a decrease in the ejection fraction (EF), systolic shortening (SS) of LV, end-diastolic LV pressure (EDLVP) and high systolic and diastolic myocardial stress. In concentric remodeling and normal LV geometry impairing of the LV diastolic function by relaxation type is combined with a less pronounced increase in pre- and afterloading. While in eccentric hypertrophy with and without dilatation of the LV, the pseudonormal type of diastolic dysfunction correlates with high pre- and afterloads.

These changes are combined with a decrease in the quality of life (MLHFQ scale). The maximum decrease in the quality of life (75.82 points on the MLHFQ scale) was found in eccentric hypertrophy with dilation.

Thus, in patients undergoing Q myocardial infarction, cardiac remodeling is characterized by the formation of eccentric hypertrophy with dilatation of 27.5% and without LV dilatation of 23.5%; normal heart geometry in 25% and concentric hypertrophy in 24% of cases.

In patients undergoing Q myocardial infarction, a symptom of maladaptive remodeling of the left ventricle, along with characteristic clinical symptoms, are systolic dysfunction, a decrease in the index of the relative thickness of the walls of the left ventricle, and restrictive type of its diastolic dysfunction. Disadaptive model of the left ventricle should be considered as remodeling by type of eccentric hypertrophy with dilation [1,8,17].

When studying the level of cytokines in patients undergoing Q myocardial infarction, an increase in TNF-α, IL-6 levels was noted in comparison with the control (Fig. 1). Intergroup studies revealed an increase in TNF-α and IL-6 in the group of eccentric hypertrophy and LV dilation.
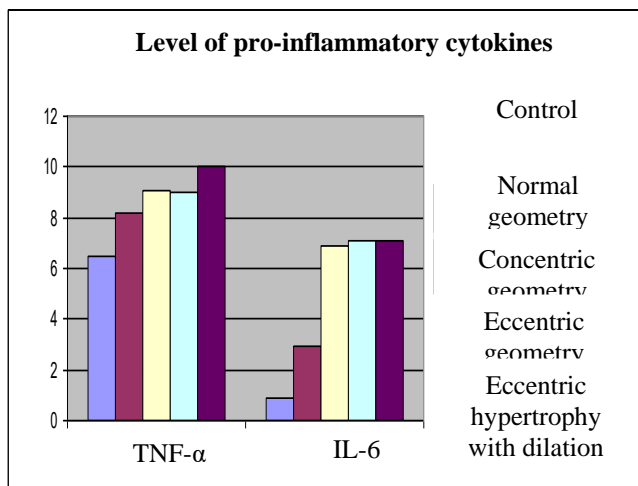
Note: * - differences with the normal geometry of the LV p <0.05; # - differences with control p <0.05.

Fig. 1. The level of proinflammatory cytokines in the serum.

Thus, a combination of dilatation, myocardial hypertrophy, systolic, diastolic LV dysfunction and negative effects on the myocardium of pro-inflammatory cytokines contributes to the progression of chronic heart failure.

To assess the degree of influence (determination of independent prognostic factors) of the parameters studied on the progression of chronic heart failure and cardio hemodynamic disorders in post infarction myocardial remodeling in patients with FC III by NYHA, multivariate regression analysis was performed.

Table 2
Regression coefficients in the multivariate model for predicting chronic heart failure

Indicators	regression coefficient - beta	Standard error β	Relative risk (95% of the confidence interval)	P
ФВ<40, %	0,52	0,1	4,3 (2,66; 8,23)	0,000011
Eccentric hypertrophy with dilation	0,25	0,03	2,78 (1,2; 4,57)	0,0031
TNF - α	0,08	0,04	2,3 (1,1; 3,9)	0,04578
IL-6	0,09	0,03	1,55 (0,63; 2,61)	0,01093
MLHFQ	0,2	0,05	1,75 (0,84; 2,96)	0,0001

The results of the regression analysis showed (Table 2) that the most closely associated with the prognosis of chronic heart failure in patients with FC III in the NYHA was a decrease in EF <40%.

The accuracy of prediction of chronic heart failure in post-infarction myocardial remodeling increased with the addition of data on eccentric hypertrophy with dilation, TNF-α, data on the decline in the quality of life (MLHFQ scale), and IL-6.

Thus, step-by-step regression multivariate analysis allowed to establish that among the studied parameters of the prognosis of chronic heart failure in patients of FC III by NYHA, the most significant factors were: decrease in EF <40%, eccentric hypertrophy with dilation, systolic and diastolic dysfunction of the left ventricle, increase in TNF α and IL-6 (P>0.05). These changes are combined with a decrease in the quality of life (MLHFQ scale). The maladaptive model, an eccentric hypertrophy with dilation, is also independently associated with the prognosis of the clinical course of post-infarction heart failure.

Conclusion: Understanding the complex mechanisms of development of chronic heart failure in patients with postinfarction myocardial remodeling in combination with the clinical picture, cardiohemodynamic indicators and laboratory markers will allow not only to identify the maladjusted LV model in the early stages of the disease, but also to develop new pathogenically based treatment methods for this pathology.

REFERENCES

[1] Ahmedov I. et al. features of hyperreninemic aldosteronism in hypertension patients with metabolic syndrome: 87 //European Journal of Preventive Cardiology. – 2016. – T. 23. – №. 1. – C. S16.

[2] Alyavi A.L. et al. Efficacy of combined antihypertensive therapy in patients with metabolic syndrome //clinical cardiology. – 111 river st, hoboken 07030-5774, nj usa : wiley-blackwell, 2016. – т. 39. – с. 12-12.

[3] Alyavi A.L. et al. Combined Therapy With Telmisartan And Amlodipine On Blood Pressure, Echocardiographic Parameters And Microalbuminuria In Patients With Metabolic Syndrome //Journal of Hypertension. – 2018. – T. 36. – C. e85.

[4] Alyavi B. et al. Influence of telmisartan and amlodipine combination on blood pressure, echocardiographic parameters and microalbuminuria in patients with metabolic syndrome //nephrology dialysis transplantation. – great clarendon st, oxford ox2 6dp, england : oxford univ press, 2018. – т. 33. – с. 374-+.

[5] Alyavi B. et al. Role of pro-inflammatory cytokines in metabolic syndrome //allergy. – 111 river st, hoboken 07030-5774, nj usa : wiley, 2018. – T. 73. – C. 562-562.

[6] Andreeva E.O. Features of the functional state of the vascular wall endothelium and the nature of heterogeneous vasodilation in patients with coronary artery disease II-III functional class of angina of exertion / E.O. Andreeva, L.B. Koryakin et al. // Siberian Medical Journal. - 2008. - №3. Pp. 17-21.

[7] Babaev M. et al. P2533 Influence of l-arginine aspartate on vascular markers in hypertensive patients with metabolic syndrome //European Heart Journal. – 2018. – T. 39. – №. suppl_1. – C. ehy565. P2533.

[8] Badger A.L. The regulatory role of the endothelium and some aspects of the effect of pharmacotherapy on its function / LA. Badger et al. // Modern technologies in medicine. - 2011. - №3. - p. 142-146.

[9] Blum A. Role of cytokines in heart failure/ A. Blum, H. Miller // Am.Heart.J. -1998. - Vol.135. -P.181-186.

[10] Brunner H. Endothelial function and dysfunction. Part II: Association with cardiovascular risc factors and diseases. A statement by the working. Group on Endothelins and Endothelial Factors on the European society of Hypertension / H. Brunner et al. // J. Hypertens. – 2005. - № 23 (2). – P. 223-246.

[11] Koziolov N.A. Assessment of vascular remodeling in patients with coronary heart disease, depending on the severity of chronic heart failure / N.A. Koziolov, A.I. Chernyavina et al. // Heart failure. - 2010. - №2 (58). - pp. 83-88.

[12] Kremneva, L.V. Interleukin-6 and cell adhesion molecules: association with risk factors and prognosis of coronary heart disease / L.V. Kremneva, ST. Shalaev // Clinical Pharmacology and Therapy .- 2004.- №13.-C. 78-84.

[13] Lutfullayevich A. A. et al. GW28-e0699 Cardiovascular risk stratification and gender differences in hypertensive patients with metabolic syndrome //Journal of the American College of Cardiology. – 2017. – T. 70. – №. 16 Supplement. – C. C138-C139.

[14] Lyutfullayevich A. A. et al. Relationship between hemodynamic parametres and nppa, nppb, npr3 genes polymorphism in patients with ischemic heart disease //International scientific review. – 2017. – №. 7 (38).

[15] Pan J. P. et al. The value of plasma levels of tumor necrosis factor-alpha and interleukin-6 in predicting the severity and prognosis in patients with congestive heart failure // J. Chin. Med. Assoc. 2004. - Vol. 67, N 5. - P. 222-228.

[16] Parkhomenko Yu.V. Features of the function of the ventricles of the heart and endothelium in gerontological patients with stable exertional angina during the formation of chronic heart failure / Yu.V. Parkhomenko, Yu.Yu. Kofman, M.V. Chistyakov // Zabay medical report. - 2007. - №2. - p. 8-12.

[17] 17. Shevchenko A.Yu. Endothelium - the structural basis of the circulatory system: the history of the problem / Yu.L. Shevchenko, P.E. Astashev, S.A. Matveev, V.G. Gudymovich // Bulletin of the National Medical and Surgical Center. N.I. Pirogov. - 2011. - Vol. 6. - №2. - p. 9-15.

[18] 18. Sukmanova I.A. Indicators of endothelial function, morphofunctional parameters of the heart and metabolic status in diastolic heart failure in patients of different age groups / I.A. Sukmanova, D.A. Yakhontov, T.I. Pospelova // Cardiology and Cardiovascular Surgery. - 2012. - №3. - pp. 72-75.

[19] 19. Usarov M. et al. Ps 11-56 Efficacy Of Combination Therapy Using Nebivalol And Trimetazidine In Hypertensive Patients With Metabolic Syndrome And Stable Angina //Journal of Hypertension. – 2016. – T. 34. – C. e349.

[20] 20. Uzokov J. et al. Influence of combination therapy of rosuvastatin and telmisartan on vascular and metabolic profile in hypercholesterolemic patients with metabolic syndrome //Atherosclerosis. – 2017. – T. 263. – C. e241.

[21] 21. Wang J. et al. Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy // J. Am. Coll. Cardiol. 2007. -Vol. 49,N l.-P. 88-96.